

Attorney Docket No. P67341US0
Serial No.: 09/926,589

Remarks/Arguments

Claims 17-24 are presented, hereby, in place of claims 9-16, cancelled hereby without prejudice or disclaimer.

Claims 17-24 correspond to claims 9-16, respectively, revised to more clearly define the invention.

Claims 9-16 were rejected under 35 USC 112, ¶2, for allegedly being indefinite. Reconsideration is requested.

Any stray marks that appear in claims 9-16 were inadvertent and are eliminated by the instant amendment.

By the instant amendment the identity "A" in claim 9 is replaced by "III" in present claim 17, as, also, identified in the specification (page 3).

The language

R₁ is (C₁-C₃) alkyl or (C₂-C₈) mono- or polyhydroxyalkyl and R₂ is (C₂-C₈) mono- or polyhydroxyalkyl or else R₁ is H and R₂ is (C₂-C₈) mono- or polyhydroxyalkyl or a group of formula A

in claim 10 is not rendered indefinite by the phrase "or else." The phrase "or else" clearly indicates that the limitation *following* the phrase is an alternative of the limitation *preceding* the phrase. In order to expedite prosecution, however, the language at issue in claim 10 is changed in corresponding replacement claim 18 to read:

R₁ is H, (C₁-C₃) alkyl, or (C₂-C₈) mono- or polyhydroxyalkyl,
when R₁ is (C₁-C₃) alkyl or (C₂-C₈) mono- or polyhydroxyalkyl, R₂ is (C₂-C₈) mono- or polyhydroxyalkyl, and
when R₁ is H, R₂ is (C₂-C₈) mono- or polyhydroxyalkyl or a group of formula A.

Claim 13 is revised hereby, as claim 21, to be dependent on an active claim, i.e., present claim 17.

Independent claim 15 is rewritten hereby as a dependent claim, i.e., claim 23, which is dependent on claim 17. Thereby, antecedent basis is found in replacement claim 23 for the variable "R" appearing in the rejected claim.

As for the term "racemic compound," it is not indefinite as alleged in the statement of rejection. The term has a well defined accepted meaning in the art, e.g., in *Basic Terminology*

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of Stereochemistry (IUPAC Recommendations 1996) <http://www.chem.qmul.ac.uk/iupac/stereo/>,
Entries beginning with R and S (<http://www.chem.qmul.ac.uk/iupac/stereo/>) (copy attached
hereto as "Appendix," pages i and ii) (*emphasis in original*):

Racemic Compound

A crystalline *racemate* in which the two *enantiomers* are present in equal
amounts in a well defined arrangement within the lattice of a
homogeneous crystalline addition compound.

The correct test for indefinite claim language is whether one of ordinary skill in the art
would be confused as to the meaning of subject matter defined by the language at issue. *In re*
Kroekel, 183 USPQ 610 (CCPA 1974). According to the statement of rejection, *racemic*
compound renders the claims "confusing"; "what stereoisomers" are covered by the recited
racemic compound allegedly being "unclear" (Office Action, page 3) (*emphasis added*). The
aforesaid reasoning supporting the rejection concerns the scope (breadth) of "racemic
compound," not its definition.

However, concern about the scope of the language at issue has no bearing on whether the
language renders the claims indefinite under § 112, ¶ 2, since claim "breadth is not to be equated
with indefiniteness." *In re Miller*, 169 USPQ 597, 600 (CCPA 1970). Although an
"undoubtedly large number" of embodiments might fall within the scope of a generic expression
"the expression is not for that reason indefinite," *In re Skoll*, 187 USPQ 481, 482 (CCPA 1975),
and whether a particular embodiment is covered by the expression "is rendered no less certain
by the large number." 187 USPQ at 483. Since the rejection as applied in connection with the
limitation "racemic compound" is based on reasoning "not to be equated with indefiniteness,"
600 USPQ at 600, the rejection as so applied cannot be maintained.

Claims 15 and 16 were rejected under 35 USC 102(e) for alleged lack of novelty based
on US6187285 (Meyer). Reconsideration is requested.

For anticipation under § 102 to exist, each and every claim limitation, as arranged in the
claim, must be found in a single prior art reference. *Jamesbury Corp. v. Liton Industrial*
Products, Inc., 225 USPQ 253 (Fed. Cir. 1985). The absence from a prior art reference of a
single claim limitation negates anticipation. *Kolster Speedsteel A B v. Crucible Inc.*, 230 USPQ

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81 (Fed. Cir. 1986). A reference that discloses "substantially the same invention" is not an anticipation. *Jamesbury Corp.* To anticipate the claim, each claim limitation must "identically appear" in the reference disclosure. *Gechter v. Davidson*, 43 USPQ2d 1030, 1032 (Fed. Cir. 1997) (*emphasis added*). To be novelty defeating, a reference must put the public in possession of the identical invention claimed. *In re Donahue*, 226 USPQ 619 (Fed. Cir. 1984).

Claims 23 and 24 which replace rejected claims 15 and 16, respectively, are dependent on present claim 17. Claim 17 is limited to the "racemic compound" of stereoisomers represented in the structure identified as "formula III." Being dependent on claim 17, claims 23 and 24 are limited to the same stereoisomers represented in "formula III" of claim 17.

The statement of rejection alleges that the compound described in Meyer: Example 4 (Meyer, columns 23-24) fully meets claims 15 and 16. Replacement claims 24 and 23, however, are limited to the stereoisomeric compound of "formula III," which is not mentioned in Meyer in connection with the Example 4 compound, or anywhere else in the reference. Accordingly, limitations on claims 24 and 23 being absent from Meyer, anticipation of claims 24 and 23 is negated, *Kolster Speedsteel A B, supra*, and, so, claims 24 and 23 are not subject to rejection under 35 USC 102(e) based on Meyer.

Moreover, claims 15 and 16 are not fully met by the compound described in Meyer Example 4. The rejected claims are limited to a "racemic compound." As such, the claims are limited to a "crystalline *racemate* in which the two *enantiomers* are present in equal amounts in a well defined arrangement within the lattice of a homogeneous crystalline addition compound." *Basic Terminology of Stereochemistry, supra*. Accordingly, limitations on claims 15 and 16 being absent from Meyer, anticipation of claims 15 and 16 based on Meyer is negated, *Kolster Speedsteel A B, supra*. Since present claims 24 and 23 maintain the "racemic compound" limitation of claims 15 and 16, claims 24 and 23 are likewise not anticipated by the reference.

The statement of rejection maintains that, since "racemic compound" appears in the claim preamble of claims 15 and 16, it is not a limitation on the claims. The statement of rejection is mistaken.

A preamble limitation encompasses *material limits on claim scope* in addition to the limitations recited in the body of the claim. *Corning Glass Works v. Sumitomo Electric U.S.A.*,

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Inc., 9 USPQ2d 1962 (Fed. Cir. 1989). Where words in the preamble are necessary to the meaning of the claim, "they are deemed limitations of the claim." *Gerber Garment Technology Inc. v. Lectra Systems Inc.*, 16 USPQ2d 1446 (Fed. Cir. 1990). The recitation in a claim preamble can limit the claim so as to define over the prior art. *In re Stencel*, 4 USPQ2d 1071 (Fed. Cir. 1987).

Claims 9-12, 15, and 16 were rejected under 35 USC 103(a) for alleged lack of non-obviousness based on Meyer combined with US6177562 (Uggeri). Reconsideration is requested.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). A "ground of rejection is simply inadequate on its face . . . [when] the cited references do not support each limitation of [the] claim." *In re Thrift*, 63 USPQ2d 2002, 2008 (Fed. Cir. 2002). When conducting an obviousness analysis, "all limitations of a claim must be considered in determining the claimed subject matter as is referred to in 35 U.S.C. 103 and it is error to ignore specific limitations distinguishing over the [prior art] reference." *Ex parte Murphy*, 217 USPQ 479, 481 (PO Bd. App. 1982).

According to the statement of rejection, it is specifically considered that Uggeri teaches racemic mixtures of certain substituted DOTA analogues useful as contrast agents for methods of MRI. This analysis of the content of reference is incorrect.

The reference Uggeri aims at compounds derived from DOTA according to formula (I) and (II) both in the racemic and optically active forms useful as contrast agents.

The statement of rejection recognizes that these compounds are different from those covered by the presently pending claims.

Further, it is respectfully submitted that Uggeri does not teach a racemic mixture as claimed of those different compounds useful as contrast agents.

Indeed, the contrast agent according to claim 9 recites a racemic mixture of two specific enantiomers, i.e., the RRRR/SSSS enantiomers.

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However, the reference Uggeri does neither mention or suggest any one of these enantiomers, alone or as a racemic mixture. It only generally alleges that the claimed compounds may be useful either in a racemic or in optically pure form.

The only specific disclosure of a racemic mixture in the reference Uggeri regards the compound of example 2B. This compound is said to be obtained under the form of a mixture of *"a couple of diastereomers, each being a racemic mixture"* (col. 22 1.37-39).

For memory, the mirror image of a chiral compound is its enantiomer, while diastereomers, which exist for compounds having more than one chiral center, are stereoisomers that are not mirror images. A racemic mixture is a 1:1 mixture of two enantiomers.

In this context, we understand that the term *"a couple"* means at least two. Consequently, the compound disclosed by the Uggeri reference contains at least two racemic mixtures of two enantiomers each, in opposition to the racemic mixture recited in claim 1, which comprises only one racemic mixture, thus composed of two enantiomers, which according to the above definitions are not diastereomers.

In fact, it is considered that the term *"a couple"* would have been understood by the skilled reader as meaning several diastereomers. Indeed, the compound disclosed in the reference Uggeri possesses four chiral centers and thus the principal $2^4 = 16$ stereoisomers. According to the reference Uggeri, there is no purification step or asymmetric reaction step. It may thus be expected that the reaction product comprises substantially all stereoisomers, this mixture having however no measurable enantiomeric excess, i.e., no overall optical rotatory power properties. This leads to the problems the claimed invention intends to solve, that is the lack of reproducibility in terms of effectiveness and toxicity between two successive manufacturing batches (see application, p. 21. 17-24).

The reference Uggeri fails to point out any of these problems and further does not provide any hint to the solution according to the invention. Consequently, it could not render the claimed invention obvious.

Claims 13 and 14 are not among the claims identified in the prior art rejections of record. i.e., the rejections under §102(e) and §103(a). As such, in accordance with the instant Office

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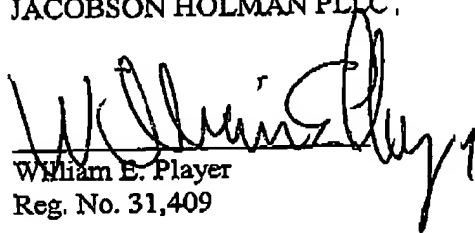
Action the subject matter in each of claims 13 and 14, represented by present claims 21 and 22,
respectively, is free of the prior art.

Favorable action is requested.

Respectfully submitted,

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Appendix

INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY
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Basic Terminology of Stereochemistry

(IUPAC Recommendations 1996)

<http://www.chem.qmul.ac.uk/iupac/stereo/>

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Basic Terminology of Stereochemistry
(IUPAC Recommendations 1996)

1. R and S

Continued from terms starting with N to Q

Contents

r, s; *R, S*; *R_p, S_p*; *R**, *S**; *rac*; Racemate; Racemic; Racemic Compound; Racemic Conglomerate; Racemic Mixture; Racemisation; *Re, Si*; *rel*; Relative Configuration; Resolution; Restricted Rotation; Retention of configuration; Ring Reversal (or ring inversion); Rosanoff Convention; Rotamer; Rotational Barrier; Rotatory Power; *RS*; *s-cis*, *s-trans*; *S*; Sawhorse Projection; *sc*; Secondary Structure; *St*; Sequence Rules; Skew; *sp*; Space Formula; Spontaneous Resolution; *SR*; Staggered Conformation; Stereochemical Formula (Stereoformula); Stereoconvergence; Stereodescriptor; Stereoelectronic; Stereoelectronic Control; Stereoformula; Stereogenic Unit (or Stereogen or Stereoclement); Stereoheterotopic; Stereoisomerism; Stereoisomerism, Planar; Stereoisomers; Stereomutation; Stereoselective synthesis; Stereoselectivity; Stereospecificity; Steric Strain; Superposability; *Syn*; *Synclinal*; *Synperiplanar*

r, s

Stereodescriptors of *pseudo-asymmetric atom*. For references see under *R, S*.

R, S

The approved designations (devised by Cahn, Ingold and Prelog) of absolute configuration at four-coordinate (quadrilignant) and six-coordinate (sexilignant) *stereogenic centres*. For the application of these stereodescriptors in systematic chemical nomenclature see R.S. Cahn, C.K. Ingold and V. Prelog, *Angew. Chem.* 78, 413-447 (1966), *Angew. Chem. Internat. Ed. Eng.* 5, 385-415, 511 (1966); and V. Prelog and G. Helmchen, *Angew. Chem.* 94, 614-631 (1982), *Angew. Chem. Internat. Ed. Eng.* 21, 567-583 (1982).

R_p, S_p See *planar chirality*.

*R**, *S** See *relative configuration*.

rac See *racemate*.

Racemate

An equimolar mixture of a pair of *enantiomers*. It does not exhibit *optical activity*. The chemical name or formula of a racemate is distinguished from those of the enantiomers by the prefix (\pm)- or *rac*- (or *racem*-) or by the symbols *RS* and *SR*.

Racemic

Pertaining to a *racemate*.

Racemic Compound

A crystalline *racemate* in which the two *enantiomers* are present in equal amounts in a well defined arrangement within the lattice of a homogeneous crystalline addition compound.

Racemic Conglomerate

An equimolar mechanical mixture of crystals each one of which contains only one of the two *enantiomers* present in a *racemate*. The process of its formation on crystallisation of a racemate is called spontaneous resolution, since pure or nearly pure enantiomers can often be obtained from the conglomerate by sorting.

Racemic Mixture (usage strongly discouraged)

The term is confusing since it has been used as a synonym for both *racemate* and *racemic conglomerate*.

Racemisation

The production of a *racemate* from a *chiral* starting material in which one *enantiomer* is present in excess.